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Although malaria and hookworm disease appear to be on the decline, another dreaded parasitic disease—schistosomiasis—is on the increase. Presently, the number of infected individuals with schistosomes is estimated to be 250 million, and even though only a small proportion of them become sick and die, schistosomiasis remains a medical problem of great significance. The high incidence of infection of man with Schistosoma mansoni, Schistosoma japonicum or Schistosoma haematobium, as well as the chronic debilitating diseases produced, places these organisms among the world’s most important infectious agents. This paper discusses the nature of immunity to schistosomiasis.

Biology of Schistosomes

Schistosomes are digenetic trematodes which undergo alternation of generations. Sexual reproduction takes place in the definitive host (man and other mammals) and an asexual reproduction in the intermediate host (snails). Eggs are passed from the body of the definitive host in the excreta (urine or feces depending on the species of schistosome). These eggs hatch in fresh water, producing free-living ciliated embryos called miracidia. The miracidia must seek, find, and penetrate a specific species of snail within a few hours in order to survive. After one month, the miracidia develop into mother sporocysts, then multiple daughter sporocysts and finally cercariae. If the snail survives the infection, the cercariae are released gradually over a duration of several months. The cercariae, free-swimming larvae, can penetrate the unbroken skin of the definitive host within minutes. During penetration, the cercariae lose their external layer and are then called schistosomula. Schistosomula migrate through the tissue into the lymph, blood vessels, and the lungs where they remain for several days. They then migrate to the liver where they mature into adult male and female schistosomes. The adult worms mate and, depending on the species, pass into the mesenteric or the vesical venules. The fertilized female worm produces 300-3,000 eggs per day. Half of these are excreted from the body, while those remaining may be trapped in the tissue.1

Schistosomiasis is mainly a disease of the young. There is a decreased passage of eggs with age, and thus a lessening of the associated symptoms. Warren1 attributed this to a gradual development of resistance rather than more reduction of exposure to infection.

Definitive diagnosis of schistosomiasis is made by recovering eggs from feces, urine or rectal biopsy specimens. Egg count can be correlated with the worm burden.2 Viable worms in the host are revealed by examining the morphology of the eggs by rectal biopsy.3 Following exposure to a given number of cercariae, the proportion of cercariae that penetrate can be determined. Worm counts can be accomplished by perfusion of the portomesenteric venous system.4

In man or experimental animals, the occurrence of various disease syndromes provides information on the immunologic status of the host, particularly in terms of hypersensitivity.1

Chronic stages of schistosomiasis, involving inflammatory and fibrotic obstruction to the flow of blood or urine, may be related to delayed hypersensitivity-type granulomatous inflammation.5,6

Immune Responses to Schistosomes

Warren1 considered the following aspects of the biology of schistosomes important immunologically:

1. The adult organisms do not replicate themselves in the definitive host although they do produce large numbers of eggs.

2. Adult schistosomes do not reside in the lumen of the gut, but within the bloodstream. The larval and embryonic (egg) phases migrate through a variety of tissue including the skin, lungs, liver, and intestinal and vesical mucosa.

3. Both the schistosomula and the eggs secrete proteolytic enzymes and other potentially antigenic materials on their passage through the tissue.

In schistosomiasis, the host is first exposed to secretions of the penetrating cercariae followed by exposure to antigenic substances. These antigenic substances are derived from live and dying cercariae that are unable to migrate past the superficial tissue. In addition, the host is subjected to secretions, excretions and somatic substances of the developing schistosomula, some of which may consequently die in the process of maturation. Eventually, the host is subjected to constant stimuli of antigenic secretions and excretions of the adult worms and embryonated eggs trapped in its tissues. The eggs are destroyed by the host, giving a continuous stimulation to its various immune mechanisms.7

The degree of host resistance differs markedly among the various species of schistosomes: S. japonicum has the widest host range; S. mansoni has fewer optimal animal hosts; and S. haematobium the least number of susceptible host species.7 Most experimentation has been performed with S. mansoni. Laboratory animals fall into three groups with regard to susceptibility to this organism: those that do not develop patent infections (egg excretion); those that develop transient infections; and those that become chronically infected.1 In the rat, worms undergo partial development, but are rapidly destroyed just before they ma-
A very substantial protective immunity to challenge develops in rhesus monkeys as a result of prior infection with the homologous species. Continuous stimulation by metabolic products of the adult worms or trapped eggs in the host’s tissue may provide antigen necessary for stimulation of protective immunity. Yogore et al studied immunity in laborers, most of whom were exposed to reinfection with S. japonicum, and found that sera from reinfected subjects revealed no changes in antibody patterns.

The appearance of precipitins in schistosome infections accompanies a marked increase in gamma-globulins which generally occurs four to six weeks after exposure of animals to cercariae. In rhesus monkeys infected with S. mansoni, total immunoglobulins usually increase within four to eight weeks after cercariae exposure. Early in infection, increase in gamma-globulins may occur in the absence of increased macroglobulin. Lewert and Mandlowitz reported that the increase in gamma-globulins occurred simultaneously with tissue damage caused by egg deposition. Jachowski et al stated that most of the gamma-globulins produced during infection were nonspecific and only a relatively small portion could be shown to be directed at schistosome-produced antigens. Warren administered gamma-globulin to children with early stage established infections and found that gamma-globulin neither reduced output of eggs by the infected children nor prevented the development of new infection in uninfected children.

Transplacental passage of specific antibody has been shown in schistosomiasis. However, it has been postulated that it is unlikely that the presence of the antibody in the new-born has any significance in protective immunity since passive transfer experiments have been successful. Antibody levels are not high in the offspring and the degradation of antibody proceeds at such a rate that little would remain at the initial exposure of the individual infant.

Existence of immunity in the presence of an active adult worm was labeled by Smithers and Terry as concomitant immunity. By this process, incoming schistosomula are destroyed by immune response of the host while the adult worm itself is not affected. Smithers suggested that the presence of host material on the surface of the worm may explain the mechanism of concomitant immunity. Sell and Dean demonstrated the presence of mouse-like antigens on the surface of schistosomula and adult S. mansoni, but not on the cercaria. Schistosomula incubated with mouse tissue in vitro or in vivo were found to absorb mouse antigens onto their surfaces. Clegg et al reported that the destruction of mouse worms did not occur upon transfer to monkeys previously immunized against either mouse immunoglobulins or sheep red blood cells. This suggested that shared antigens are not natural enhancing antibodies or Forssman antigen. In contrast, Dean and Sell demonstrated the presence of Forssman antigen on the surface of schistosomula incubated with mouse or sheep erythrocytes and on adult mouse worms.

Alternatives to the host antigen hypothesis may explain how older schistosomes are protected against immune reactions which kill young worms: (1) Site of infection is important. Worms may only be vulnerable in the skin, lungs, or liver, but not in mesenteric veins where adult worms live. (2) Rapid turnover of tegument may play a role in rapid repair of immune damage in older worms. The tegumental outer membrane of the cercariae are trilaminated, while the adult worm has a seven layered membrane. Formation of this seven layered membrane in the adult worm begins immediately after the cercaria has penetrated the vertebrate host. (3) Antigens changed or lost from the surface of schistosomula (similar to antigen variation in trypanosomes and malarial organisms).

Newsome demonstrated in vitro that schistosomula incubated in immune serum plus leukocytes were rapidly killed. Movement of the worms was slowed, leukocytes adhered to their surfaces, and the helminths died. It was suggested that this adherence phenomenon, while attributed to an opsonin in the serum, did not occur if the cells and organisms were kept in motion. In hibernating animals, the immobilized adult worms were found in the liver where they were invaded by leukocytes and were rapidly destroyed.

Capron et al found that the peritoneal adherent cells of normal rats, incubated in serum of rats immune to S. mansoni infection, became strongly adherent to S. mansoni schistosomula maintained in vitro. Electron microscopy revealed that the adherent cells were macrophages. Capron et al suggested that the factors in immune serum responsible for the macrophage adhesion were specific anti-schistosome IgE antibodies. Dean et al showed that neutrophils added to antiserum killed schistosomula in vitro.

Literature Cited